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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,434	11/18/2003	Charlotte Alback Thru	22460-010001 / 1015US1	7002
26161 7590 07/09/2008 FISH & RICHARDSON PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022				
EXAMINER VIVLEMORE, TRACY ANN				
ART UNIT		PAPER NUMBER		
1635				
NOTIFICATION DATE		DELIVERY MODE		
07/09/2008		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Office Action Summary

Application No.

10/717,434

Applicant(s)

THRUE ET AL.

Examiner

Tracy Vivemore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2007 and 25 March 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43, 47-51, 53 and 55-96 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 43, 47-51, 53 and 55-96 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Claim Rejections - 35 USC § 103

Claims 43, 47-51, 53 and 55-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wahlestedt et al. in view of Crooke (both of record).

The claims are directed to oligonucleotides comprising alternating regions of locked and non-locked nucleic acids, wherein a first region of non-locked nucleotides has a length of 4-20 bases. In specific embodiments the claims are directed to specific nucleotides wherein the length of each region is defined, the locked nucleic acids are oxy-LNA, the internucleotide linkages may be modified, and the non-locked nucleotides comprise deoxynucleotides.

Wahlestedt et al. teach antisense oligonucleotides having LNA and non-LNA segments wherein the LNA includes oxy-LNA and the non-LNA sequences are DNA, RNA and analogues. Page 8 describes that the oligonucleotides of the invention comprise patterns of alternating locked and non-locked nucleotides of varying lengths that may comprise internucleotide linkages such as phosphorothioates. Wahlestedt teaches that the pattern of X-Y-X can be repeated, as indicated by the integer q, and because the integers m and p can be 0, this teaches oligonucleotides with the pattern

X-Y-X-Y, meeting the limitations of the claims. Wahlestedt et al. do not teach sequences wherein the length of the non-locked nucleotides is 4-20.

It was well-known in the art at the time the invention was made to produce oligonucleotides of different lengths and modification patterns in order to optimize their properties. See for example Crooke, who teaches the use of gapmer oligonucleotides as antisense therapeutics. At example 22, columns 48-49, Crooke tests several sequences of gapmers and that the best performing sequences have unmodified nucleotide regions of at least 5 nucleotides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the oligonucleotides taught by Wahlestedt et al. in order to produce oligonucleotides having a sequence of non-locked nucleotides of 4-20 nucleotides and would further be obvious to modify the oligonucleotides to have both locked and non-locked regions of specific lengths. Based on the well-known practice in the art of optimization that is exemplified by Crooke, one of ordinary skill in the art would be motivated to modify the invention of Wahlestedt et al. to produce antisense oligonucleotides wherein the individual segments have particular lengths in order to produce an antisense oligonucleotide having the necessary degree of specificity and stability suitable for their particular application. Additionally, MPEP section 2144.05 describes that routine optimization or experimentation of what is known in the prior art supports a prima facie case of obviousness. One of ordinary skill in the art would have had a reasonable expectation of success in producing antisense oligonucleotides having the specific lengths recited in the instant claims because it is routine in the art of

nucleic acid synthesis to produce oligonucleotides of any desired sequence length and configuration.

Thus, the invention of claims 43, 47-51, 53 and 55-96 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the rejection by citing *Metabolite Laboratories, Inc. v. Laboratory Corporation of America Holdings* to argue that prior art references disclosing a genus do not inherently disclose all species within that genus and conclude that because Wahlestedt discloses only two specific oligonucleotides of patterns other than XYXY, Wahlestedt does not disclose oligonucleotides having the formula XYXY.

The examiner does not dispute that *Metabolite Laboratories, Inc. v. Laboratory Corporation of America Holdings* finds that generic disclosure is not an inherent disclosure of all species, but notes that this ruling was made in the context of whether a reference was anticipatory under 102. The rejection of record is for obviousness, not anticipation. It is further noted that applicants' claims are not to a species, but like Wahlestedt are directed to a genus of oligonucleotides.

Applicants argue one of ordinary skill in the art would not use the teachings of Crooke to modify the teachings of Wahlestedt because the oligonucleotides of each reference are designed for different purposes. Applicants argue Wahlestedt teaches oligonucleotides that hybridize to RNA and recruit RNase H to cleave the RNA while Crooke teaches oligonucleotides that hybridize to RNA and form double-stranded RNA

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like structures cleaved by double-stranded RNase enzymes and conclude that due to these different mechanisms those in the art would not turn to Croke to modify the oligonucleotides of Wahlestedt.

This is not persuasive because Croke is not relied upon to teach oligonucleotides acting by any particular mechanism, but to demonstrate that the optimization of oligonucleotide length and structure was a matter of simple experimentation regularly engaged in by those in the art. While it is correct the specific oligonucleotides taught by Croke contained ribonucleotides instead of deoxynucleotides, those in the art would clearly recognize that this minor difference is not relevant to the issue at hand; the routine nature of optimization of oligonucleotide lengths and patterns. Croke himself teaches at the beginning of example 22 that this example takes its cue from previous work with deoxynucleotide oligomers, teaching that:

"Structure activity analyses of antisense oligonucleotides specific for codon 12 of the Ha-ras oncogene containing various 2'-sugar modifications were reported by Monia, et al... Following a similar protocol, stretches of ribonucleotides were introduced into the center of 17 base 2'-methoxy oligoribonucleotides targeting Ha-ras mRNA to form 2'-methoxy-2'-hydroxy-2'-methoxy phosphorothioate oligoribonucleotide "gapped" chimeric compounds that have varying ribonucleotide content in the central gap segment..."

Applicants further argue that because there is no mention of LNA in Croke one skilled in the art would not turn to Croke for suggestions on how to optimize the number of nucleotides in the various portions of the oxy-LNA containing oligonucleotides of Wahlestedt. Applicants appear to be arguing that because Croke does not teach all limitations of the claims there would be no reason to combine

Wahlestedt and Crooke. This is not persuasive because in a rejection based on 103 no single reference is required to teach all limitations.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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